

ATTACHMENT II - New Claims 59-116

59. A pharmaceutical composition for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.

60. The pharmaceutical according to claim 59 further comprising an additional Compound.

D2 61. The pharmaceutical composition according to claim 59 comprising an additional compound having an additional pharmaceutical effect.

62. A pharmaceutical composition according to Claim 60 wherein the additional compound is selected among carriers, solvents and emulgators.

63. A pharmaceutical composition according to Claim 59, wherein the analog of somatostatin is Octreotide.

64. A pharmaceutical composition according to Claims 59, wherein the analog of somatostatin is Vapreotide.

65. A pharmaceutical composition according to Claim 59,
wherein the analog of somatostatin is Lanreotide.

66. A pharmaceutical composition according to Claim 59,
wherein the analogs of somatostatin are Cyclopeptide somatostatin
analogues selected among

Cyclo(Pro-Phe-D-Trp-Lys-Thr-Phe]

Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe

Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]

Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]

Cyclo[Pro-Phe-D-Trp-Lys- α -aminobutyric-Phe]

Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]

Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]

Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]

Cyclo(Pro-Phe-D-Trp-Lys-Thr(Bzl)) (Bzl = (a))

Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]

Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]

Cyclo(Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-

Tyr-Thr-Ser] [SEQ ID NO 1] (Ahep = (b))

Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]

Cyclo(Ahep-Phe-D-Trp-Lys-Thr]

Cyclo(Ahep-Phe-D-Trp-Lys-Ser(Bzl)]

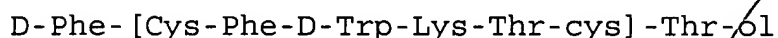
Cyclo [Ahex-Phe-D-Trp-Lys-Thr (Bzl) (Ahex = (c))

Cyclo[Aoet-Phe-D-Trp-Lys-Thr(Bzl)) (Aoet = (d))

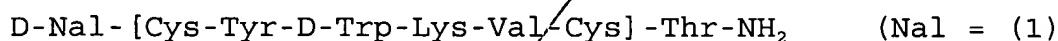
Cyclo(Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]

- (a) Bzl = benzyl
- (b) Ahep = 7-aminoheptanoyl
- (c) Ahex = 6-aminohexanoyl
- (d) Aoct = 8-amino-octanoyl.

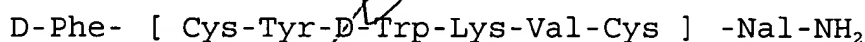
67. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



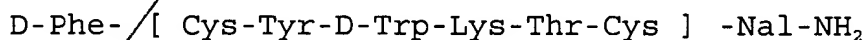
68. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



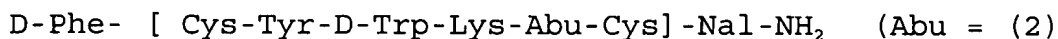
69. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



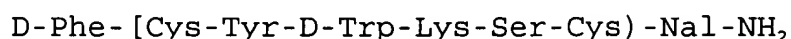
70. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



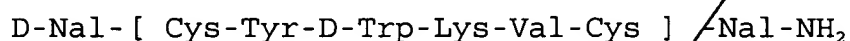
71. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



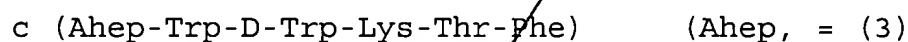
72. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



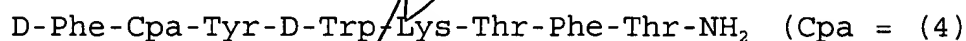
73. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



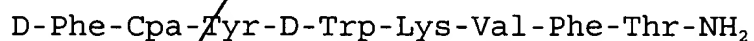
74. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



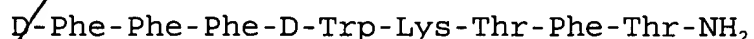
75. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



76. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



77. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



78. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂

79. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂

80. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH₂

81. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂

82. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂

83. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂

84. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analogs are polypeptides of the formula:

X-Lys-Asn-Phe-Phe-A-Lys-Thr-Phe-Thr-Ser-Y

wherein A is L- or D-Trp,

X is H-(Aeg)_m-Cys- or H-(Aeg)_m-Ala-Gly-Cys-,

Y is -Cys- (Aeg)_n-OH or

X and Y taken together are a 2-amino ethyl-glycyl group in
the ring position and

m and n are 0, 1, 2, provided that

m and n are at least 1,

and their cyclic disulfide derivatives.

85. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analogs are peptides of the formula:

Bmp-Lys-X-Phe-Phe-trp-Lys-Thr-Phe-Thr-Y-Cys-OH
3 4 5 6 7 8 9 10 11 12 13 14 [SEQ ID NO 2]

in which

Bmp represents the desaminocysteine radical,

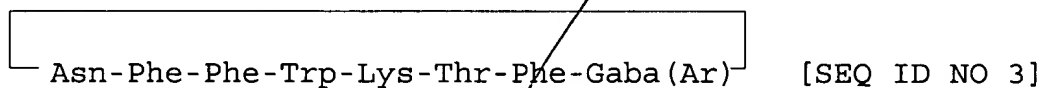
X represents Asn,

trp represents D-Trp that may be substituted
in the benzene ring by a halogen atom, and

Y represents the radical of an alpha-(lower
alkyl) amino- (lower alkyl)-carboxylic acid
having a minimum of 4 and a maximum of 8

carbon atoms, in which the two lower alkyl radicals can be connected to one another with a single C-C bond, an oxygen atom or a sulphur (II) atom.

86. A pharmaceutical composition according to Claim 59, wherein the somatostatin analogs are cyclic octapeptides of the formula:



5 6 7 8 9 10 11 12

in which

Trp represents L-Trp or D-Trp, in which the benzene ring may be substituted by a fluorine atom, and

Gaba(Ar) represents the residue of a α -aminobutyric acid substituted by a cyclic hydrocarbyl radical Ar selected from the group consisting of cyclohexyl; phenyl optionally substituted by halogen, nitro or phenoxy; and naphthyl optionally substituted by halogen.

87. A pharmaceutical composition according to Claim 59, wherein the somatostatin analogs are compounds of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R₈-Ala-Pro-Arg-Glu-Arg-Lys-
Ala-Gly-Cys-R₁₈-R₁₉-Phe-Phe-D

-Trp-Lys-Thr-R₂₅-R₂₆-R₂₇-R₂₈-OH wherein R₈ is Met or Leu, R₁₈ is Lys or des R₁₈, R₁₉ is Asn or des R₁₉, R₂₅ is Phe or Tyr, R₂₆ is Thr or des R₂₆, R₂₇ is Ser or D-Ser and R₂₈ is D-Cys or Cys.

88. A pharmaceutical composition according to Claim 59, wherein the somatostatin analogs are compounds of formula

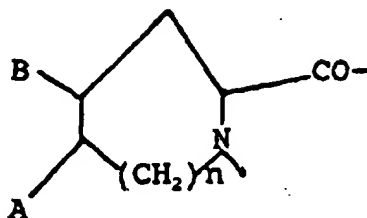
D2
H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R₈-Ala-Pro
-Arg-Glu-Arg-Lys-Ala-Gly-Cys-R₁₈-R₁₉-Phe-Phe-D-Trp-Lys

-Thr-R₂₅-R₂₆-R₂₇-R₂₈-OH wherein R₈ is Met or Leu, R₁₈ is Lys or des R₁₈, R₁₉ is Asn or des R₁₉, R₂₅ is Phe or Tyr, R₂₆ is Thr or des R₂₆, R₂₇ is Ser or D-Ser and R₂₈ is D-Cys or Cys, or the linear version thereof where the disulfide bridge is replaced by hydrogen.

89. A pharmaceutical composition according to Claim 59, wherein the somatostatin analogs are cyclic hexapeptides of the formula

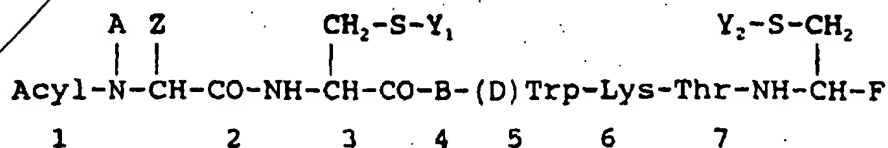
-X - Phe-D-Trp-Lys-Y-Phe

in which X represents the radical of an L-amino acid of the formula

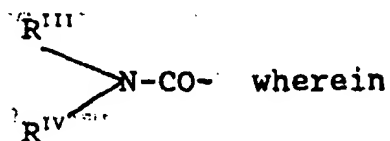


12 in which A and B are identical or different and denote alkyl having 1 to 3 carbon atoms, or A and B together represent a saturated, unsaturated or aromatic monocyclic or bicyclic structure having 3 to 6 carbon atoms, n denotes 0 or 1, and Y represents an aliphatic or aromatic L-amino acid the side-chain of which can be hydroxylated, said amino acid being selected from the group consisting of L-alanine, L-serine, L-valine, L-leucine, L-isoleucine, L-phenylalanine and L-tyrosine.

90. A pharmaceutical composition according to Claim 59, wherein the somatostatin analogs are N-acyl-polypeptides of formula,



wherein "Acyl" is a group of formula $R^I\text{CO-}$ wherein R^I is C_{1-20} ,
alkyl or phenyl; a group of formula $R^{II}\text{SO}_2\text{-}$ wherein R^{II} is C_{1-20} -
alkyl, phenyl or tolyl; a group



R^{III} and R^{IV} are each independently hydrogen

or C_{1-10} alkyl; or biotinyl,

A is hydrogen or C_{1-3} alkyl,

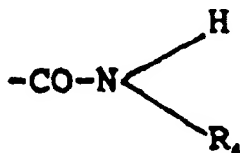
$>\text{N-CH(Z)-CO-}$ is an (L)- or (D)-phenylalanine residue
optionally ring-substituted by NO_2 or an (L) or (D) -norleucine
residue,

whereby

Z in $>\text{N-CH(Z)-CO-}$ represents the remainder of said
residue,

B is -Phe- optionally ring-substituted by NO_2 ,

F is a group of formula



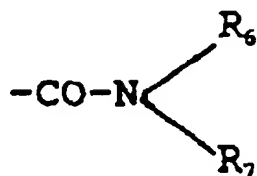
wherein R_1 is hydrogen or a group of formula

-CH(R₅)-X,

R₅ is CH₃CH(OH)-, i-butyl or benzyl

X is a group of formula -COOR₁,

-CH₂OR₂ or



wherein R₁, R₆ and R₇, are each hydrogen or C₁₋₃ alkyl, and

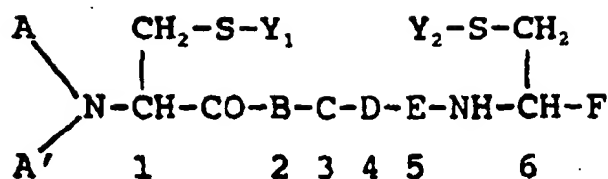
R₂ is hydrogen or the residue of a

physiologically acceptable,
physiologically hydrolysable
ester,

the group -CH(R₅)-X having the (D)- or (L)-configuration and Y₁, and Y₂ are each hydrogen or together represent a direct bond, whereby the residue resides in the 2- and 7-position each independently have the (L)- or (D)-configuration, and with the proviso that:

- i) (L)- and/or (D)-cysteine residues are present at the 2- and 7-positions only.

91. A pharmaceutical composition according to Claim 59, wherein the somatostatin analogs are polypeptides of the formula



wherein A is C₁₋₁₂ alkyl, C₇₋₁₀ phenylalkyl or a group of formula RCO-,

whereby

i) R is hydrogen, C₁₋₁₁ alkyl, phenyl or C₇₋₁₀ phenylalkyl, or

ii) RCO- is a) an L- or D-phenylalanine residue optionally ring-substituted by halogen and/or C₁₋₃ alkyl,

b) H-Asn-, or

c) H-Nle-Asn-,

the α -amino group of amino acid residues a)

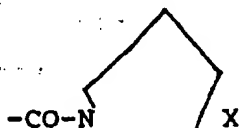
and b) and the N-terminal amino group of

dipeptide residues c) being optionally mono

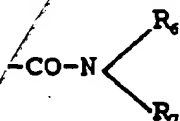
or di-C₁₋₁₂ alkylated,

A' is hydrogen or, when A is C₁₋₁₂alkyl or C₇₋₁₀phenylalkyl, also C₁₋₁₂alkyl or C₇₋₁₀phenylalkyl,
 B is -Phe- optionally ring-substituted by halogen and/or C₁₋₃alkyl,
 C is -(L)- or -(D)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen and/or C₁₋₃alkyl,
 D is -Lys- optionally α-N-methylated and optionally Σ-N-C₁₋₃-alkylated,
 E is -Thr- or -Ala- each in (D)- or (L)-form and each being optionally α-N-methylated,

F is a group of formula -COOR₁, -CH₂OR₂, -CO-N  or



wherein R₁ is hydrogen or C₁₋₃alkyl,
 R₂ is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R₃ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀-phenylalkyl,
 R₄ is hydrogen, C₁₋₃alkyl or, when R₃ is hydrogen or methyl, also a group of formula -CH(R₅)-X,
 R₅ is hydrogen, -(CH₂)₂-OH, -(CH₂)₃-OH, -CH₂-OH, -CH(CH₃)-OH, isobutyl or benzyl
 X is a group of formula -COOR₁, -CH₂OR₂ or

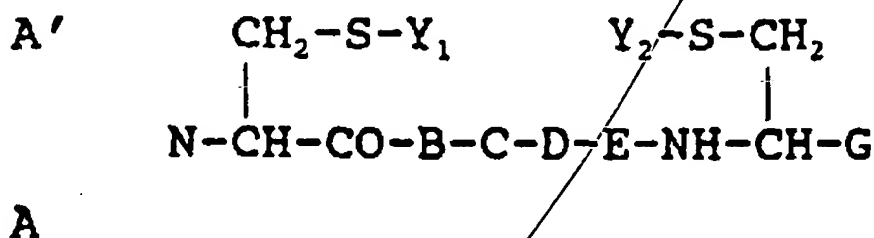


wherein

R₁ and R₂ have the meanings given above,
 R₆ is hydrogen or C₁₋₃alkyl and
 R₇ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀phenylalkyl,

the group -CH(R₁)-X having the D- or L- configuration, and Y₁ and Y₂ are each hydrogen or together represent a direct bond, whereby the residues in the 1- and 6-position each independently have the L- or D-configuration.

92. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is a compound of formula



wherein

A is C₁₋₁₂ alkyl, C₇₋₁₀ phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C₁₋₁₁ alkyl, phenyl or C₇₋₁₀ phenylalkyl or

ii) RCO- is

a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO₂, NH₂, OH, C₁₋₃ alkyl and/or C₁₋₃ alkoxy;

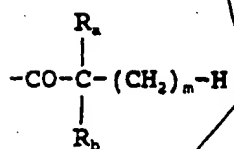
b) the residue of a natural or synthetic α-amino acid other than defined under a) above or of a corresponding D-amino acid, or

C) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

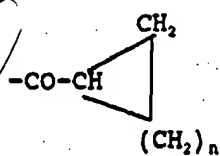
C_{1-8} alkanoyl,

A' is hydrogen,

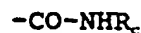
Y, and Y, represent together a direct bond or
each of Y, and Y, is independently hydrogen or
a radical of formulae (1) to (5).



(1)

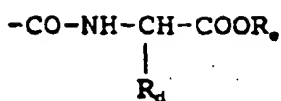


(2)

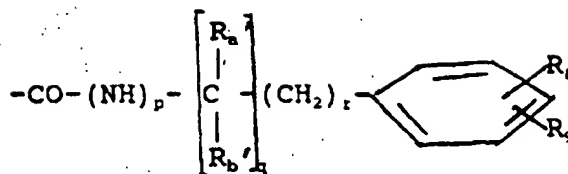


(3)

D2



(4)



(5)

wherein

R_a is methyl or ethyl

R_b is hydrogen, methyl or ethyl

m is a whole number from 1 to 4

n is a whole number from 1 to 5

R_c is (C₁₋₆)alkyl

R_d represents the substituent attached to the α-carbon atom of a natural or synthetic α-amino acid (including hydrogen)

R_e is (C₁₋₅)alkyl

R_{a'} and R_{b'} are independently hydrogen, methyl or ethyl,

R_s and R₆ are independently hydrogen, halogen, (C₁₋₃)alkyl or (C₁₋₃)alkoxy,

p is 0 or 1,

q is 0 or 1, and

r is 0, 1 or 2,

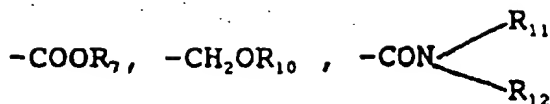
B is -Phe- optionally ring-substituted by halogen, NO₂, NH₂, OH, C₁₋₃alkyl and/or C₁₋₃alkoxy (including pentafluoroalanine), or β-naphthyl-Ala

C is (L)-Trp- or (d)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen, NO₂, NH₂, OH, C₁₋₃alkyl and/or C₁₋₃alkoxy,

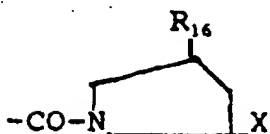
D is Lys, Lys in which the side chain contains O or S in β-position, F-Lys or δF-Lys, optionally α-N-methylated, or a 4-aminocyclohexylAla or 4-aminocyclohexylGly residue

E is The, Ser, Val, Phe, Ile or an aminoisobutyric or aminobutyric acid residue

G is a group of formula

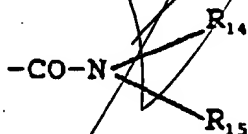


or



wherein

- R_7 is hydrogen or C_{1-3} alkyl,
 R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R_{11} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenyl-alkyl,
 R_{12} is hydrogen, C_{1-3} alkyl or a group of formula $-\text{CH}(\text{R}_{13})-\text{X}_1$,
 R_{13} is CH_2OH , $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, or $-\text{CH}(\text{CH}_3)\text{OH}$ or represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen) and
 X_1 is a group of formula $-\text{COOR}_7$, $-\text{CH}_2\text{OR}_{10}$ or



wherein

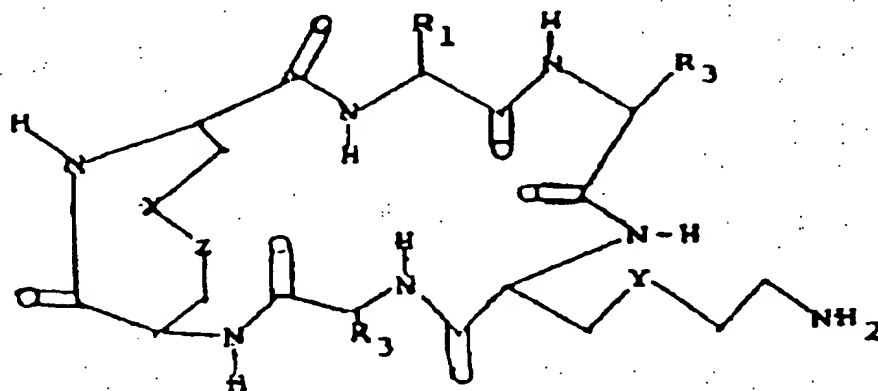
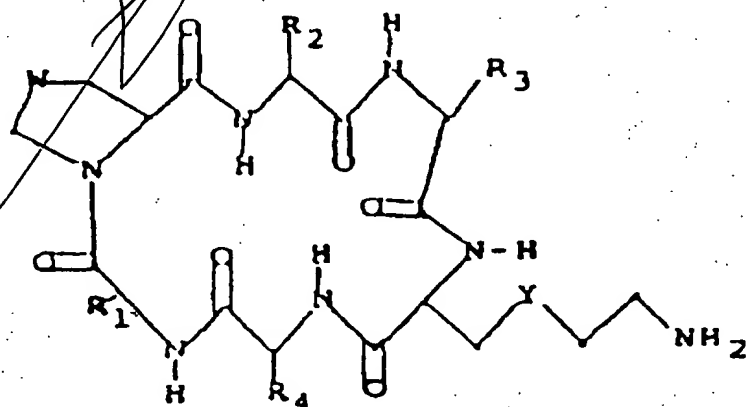
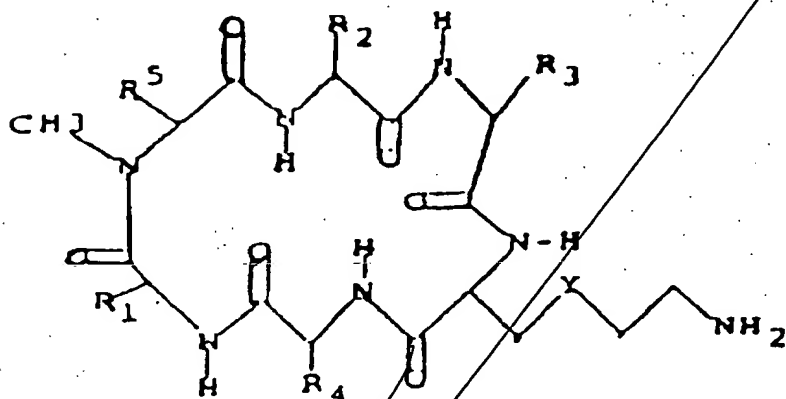
- R_7 and R_{10} have the meanings given above,
 R_{14} is hydrogen or C_{1-3} alkyl and
 R_{15} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenylalkyl, and
 R_{16} is hydrogen or hydroxy,

with the proviso that

when R_{12} is $-\text{CH}(\text{R}_{13})-\text{X}_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y_1 (4) and Y_2 (4) each independently have the (L)- or (D)- configuration.

93. A pharmaceutical composition according to Claim 59,
wherein the analog is a somatostatin analog selected from the
compounds of the following formulae



wherein

W is

one of X and Z

Y is

each of R₁ and R₂

S or (CH₂)_s, where s is 0, 1 or 2;

is S and the other is S or CH₂;

S or (CH₂)_t, where t is 0, 1 or 2;

independently of the other, is C₁₋₅ alkyl, benzyl, benzyl having one or two C₁₋₅ alkyl, halogen, hydroxy, amino, nitro, and/or C₁₋₅ alkoxy substituents, or C₁₋₅ alkyl substituted with 5- or 6-membered heterocyclic ring;

R₃ is

3-indolylmethyl, either unsubstituted or having C₁₋₅ alkyl, C₁₋₅ alkoxy or halogen substitution;

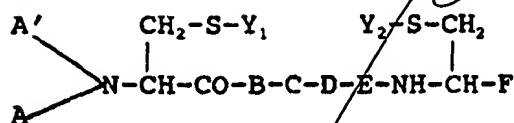
R₄

C₁₋₅ alkyl, C₁₋₅ hydroxyalkyl, benzyl, carboxy-(C₁₋₅ alkyl), amino (C₁₋₅ alkyl) or benzyl having a C₁₋₅ alkyl, halogen, hydroxy, amino, nitro and/or C₁₋₅ alkoxy substituent;

R₅ is

C₁₋₅ alkyl, benzyl, or benzyl having a C₁₋₅ alkyl, halogen, hydroxy, amino, nitro, and/or C₁₋₅ alkoxy substituent,

compounds of formula



wherein

A is C₁₋₁₂ alkyl, C₇₋₁₀ phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C₁₋₁₁ alkyl, phenyl or C₇₋₁₀ phenylalkyl, or

ii) RCO-is

a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO₂, NH₂, OH, C₁₋₅ alkyl and/or C₁₋₅ alkoxy

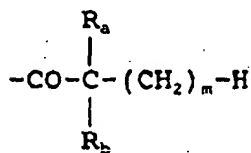
b) the residue of a natural α-amino acid other than defined under a) above or of a corresponding D-amino acid, or

c) a dipeptide residue in which the individual amino acid

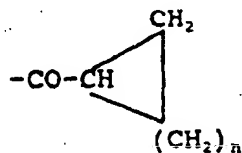
residues are the same or different and are selected from those defined under a) and/or b) above, the α -amino group or amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- $C_{1,12}$ alkylated,

A' is hydrogen or, when A is $C_{1,12}$ alkyl or $C_{7,10}$ phenylalk- also $C_{1,12}$ alkyl or $C_{7,10}$ phenylalkyl,

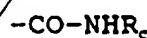
Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of the formulae



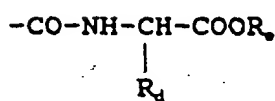
(1)



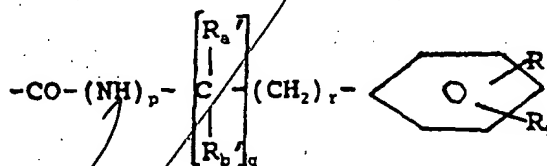
(2)



(3)



(4)



(5)

wherein R_a is methyl or ethyl

R_b is hydrogen, methyl or ethyl

m is a whole number from 1 to 4

n is a whole number from 1 to 5

R_c is $(C_{1,6})$ alkyl

R_d represents the substituent attached to the α -carbon atom of a natural α -amino acid (including hydrogen)

R_e is $(C_{1,3})$ alkyl

R_a' and R_b' are independently hydrogen, methyl or ethyl,

R_1 and R_2 are independently hydrogen, halogen, $(C_{1,3})$ alkyl or $(C_{1,3})$ alkoxy,

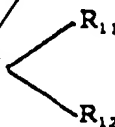
p is 0 or 1,

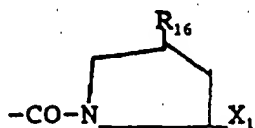
q is 0 or 1, and

r is 0, 1 or 2,

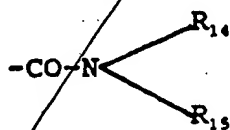
B is -Phe- optionally ring-substituted by halogen, NO_2 , NH_2 ,

OH, C₁₋₃alkyl and/or C₁₋₃alkoxy, or naphthylalanine.
 C is (L)-Trp- or (D)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen, NO₂, NH₂, OH, C₁₋₃ alkyl and/or C₁₋₃ alkoxy,
 D is -Lys-, ThiaLys, F-Lys, δF-Lys or Orn, optionally α-N-methylated, or a 4-aminocyclohexyl Ala or 4-aminocyclohexyl Gly residue,
 E is Thr, Ser, Val, Phe, Ile or an aminoisobutyric acid residue

F is a group of formula -COOR₇, -CH₂OR₁₀, -CON  or



wherein R₇ is hydrogen or C₁₋₃alkyl,
 R₁₀ is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R₁₁ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀-phenylalkyl,
 R₁₂ is hydrogen, C₁₋₃alkyl or a group of formula-CH(R₁₃)-X₁,
 R₁₃ is CH₂OH, -(CH₂)₂-OH, -(CH₂)₃-OH, or -CH(CH₃)OH or represents the substituent attached to the α-carbon atom of a natural α-amino acid (including hydrogen) and
 X₁ is a group of formula -COOR₇, -CH₂OR₁₀ or



wherein

R₇ and R₁₀ have the meanings given above,
 R₁₄ is hydrogen or C₁₋₃alkyl and
 R₁₅ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀phenylalkyl, and
 R₁₆ is hydrogen or hydroxy,
 with the proviso that
 when R₁₂ is -CH(R₁₃)-X₁ then R₁₁ is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y, 4) and Y, 4) each independently have the (L)- or (D)-configuration and compounds of the following formulae

H-Cys-Phe-(D)Trp-Lys-Thr-Phe-Cys-OH

-Asn-Phe-Phe-(D)Trp-Lys-Thr-Phe-Gaba

MeAla-Tyr-(D)Trp-Lys-Val-Pb

NMe-Phe-His-(D)Trp-Lys-Val-Ala.

94. A pharmaceutical composition according to Claim 59, wherein the analogs are Somatostatin analogs

X-Cys-D-o-Trp-E-F-Cys-Y

I

[SEQ ID 4]

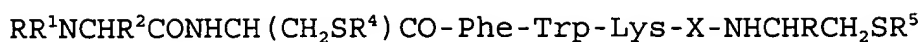
X-Cys-Lys-Asn-Phe-D-o-Trp-E-F-Phe-Thr-Ser-Cys-Y

II

I, II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R¹); R¹ = C₁-(fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH₂, NHR¹.

[SEQ ID 5]

95. A pharmaceutical composition according to Claim 59, wherein the somatostatin analogs are peptides:



[R inorg. or org. acyl group, $R^1 = H$, alkyl, $NCHR^2CO$ moiety = I.

D₂ Me(CH₂)₆CO-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol I
or D-Phe (optionally ring substituted by halo, NO₂, OH, alkyl, alkoxy); Phe, Trp, (D or L), may be ring substituted by NO₂, NH₂, OH, alkyl, alkoxy; Lys may be α-N-methylated and ε-N-alkylated; X = D- or L-α-amino acid residue optionally α-N-methylated; R¹ = CO₂H, CH₂OH, carbamoyl, R⁴ = R⁵ = H, R⁴R⁵ = bond]

96. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly

Cys-X¹-X²-Phe-Phe-D-Trp-Lys-Tys-Thr-X³-X⁴-X⁵-X⁶-OH

97. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

98. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is

c(Spacer-Phe-D-Trp-Lys-Thr)

Spacer may stand for:

- a) R,S- δ -Bn-o-AMPA
- b) R- α -Bn-Me-o-AMPA
- c) Phe-Pro

99. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:

H₂N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

[SEQ ID NO 6]

100. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:

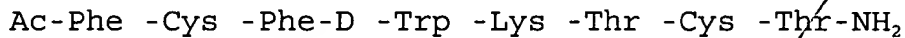
H₂N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-
Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH [SEQ ID No
7]

101. A pharmaceutical composition according to Claim 59,

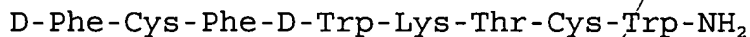
wherein the somatostatim analog is:



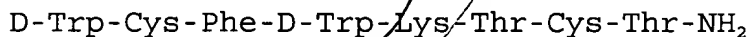
102. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



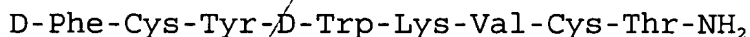
103. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



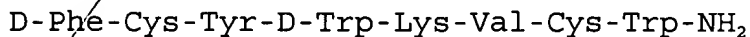
D₂ 104. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



105. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



106. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:



107. A pharmaceutical composition according to Claim 59,
wherein the somatostatin analog is:

3-(2-naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂

108. A pharmaceutical composition according to Claim 59, wherein the somatostatin analog is:

c(Aha-Phe-p-Cl-Phe-D-Trp-Lys-Thr-Phe)

Aha = 7 -amino heptanoic acid.

109. A pharmaceutical composition according to Claim 59, wherein the active ingredient is diazoxide and comprises in addition a thiazide selected among chlorothiazide, hydrochlorothiazide, trichloromethiazide and polythiazide.

110. A method for the treatment of symptoms of syndrome X by administering to a patient a pharmaceutical composition according to Claim 59 comprising a pharmaceutically effective dosage of a compound selected among somatostatin or one of its analogs, diazoxide or one of its analogs, cyclothiazide or one of its analogs and metformin.

111. A method according to Claim 110, wherein the pharmaceutically effective dosage (calculated on octreotide) does not exceed 50µ/kg/day.

112. A method according to Claim 110, wherein said dosage does not exceed 40 μ /kg/day.

113. A method according to Claims 109 wherein the analog is Octreotide which is applied in the form of an injection in a 0.9% saline solution.

114. A method according to Claim 109, wherein said dosage does not exceed 8 mg/kg/day in the treatment of the active ingredient (calculated on diazoxide) in adults, and does not exceed 15/mg/day in the treatment of children.

115. A method according to Claim 109, wherein the amount of metformin applied does not exceed 2.5 g/day divided into 2 -3 portions.

116. The method of formulating a composition containing a compound selected among somatostatin or one of its analogs, diazoxide or one of its analogs, cyclothiazide or one of its analogs and metformin in a preparation for the treatment of the risk factors of syndrome X of Reaven.

add 33